REMARKS

Claims

Claims 1, 51-57, and 64, 65, 67 are currently under examination. Claims 2–50 and 66 are cancelled without prejudice or disclaimer and claims 58-63 and 68-104 withdrawn from consideration due to restriction/election.

Claim amendments

Support for amended claim 1 can be found at, for example, page 9, lines 28-31. Claim 65 incorporates the elements of dependent claim 68. No new matter is added.

It is courteously requested that previously withdrawn claim 68, in view of the amendments thereto, be rejoined for consideration and further examined on the merits.

The claims have been further amended to use language in accordance with conventional US practice and to establish proper dependencies. The dependency of claim 67 has been amended to read claim 65.

Restriction/Objection

The claims in Group 10 (claims 71, 75, and 79), which are drawn to a method of diagnosing or treating diseases, and the claims in Group 19 (claims 83–92), which are drawn to a method for modulating the level and/or activity of a target substance in a cell, both utilize a polypeptide of the elected Group I. "If a product claim is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined." See M.P.E.P. § 806.05. Rejoinder of these claims is therefore courteously requested.

The alleged requirement that claims 1, 51-57, and 64-67 of the instant application "must be restricted to elected subject matter only" is respectfully traversed since such is not required, particularly in this case, where claims appear to be suitable for rejoinder.

Rejection under 35 U.S.C. §102(b)

The rejection of claims 1, 51-57, and 64-67 under 35 U.S.C. §102(b) as allegedly anticipated by Isaac et al. (US 6,372,211) is respectfully traversed.

In levying the anticipation rejection, the Office Action at page 10 contends that

"Issac et al. teach a L-lysine oxidase, comprising residues 120-135 of SEQ ID NO: 2" (i.e., a protein comprising any fragment of SEQ ID NO: 2). However, no structural information (i.e., polypeptide sequence) of fragments, if any, that are recited in Issac was provided. The cited reference discloses more than 55 sequences. See, the SEQUENCE LISTING disclosure of Issac et al. No sequence which allegedly anticpates the claims is identified and Applicants submit that Issac fails to disclose a sequence meeting Applicants' SEQ ID NO: 2, 4, OR 6. Additionally, the Office Action does not furnish the Applicant the methodology used in the identification of the anticipating sequence(s). Therefore, it is courteously submitted that the PTO has failed to meet its burden. Absence such guidance, there can be no anticipation. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

The rejection is moot in view of the amendments. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

The rejection of claims 1, 51-57, and 64-67 under 35 U.S.C. §112, first paragraph, due to allegedly lacking a written description and for failing to provide enablement is respectfully traversed.

At the outset, it is courteously submitted that the §112, first paragraph rejection of claims 65–68 for allegedly failing to describe the modulating substance is moot in view of the amendments. No acquiesce in the rejection is to be implied. The following arguments are provided to refute the PTO's contention that the polypeptide structures recited in Applicants' claims are large, and thus objectionable from a Section 112, first paragraph standpoint as for being allegedly inadequately described and/or lacking in enablement.

Written Description

At page 4, the Office Action alleges that "the specification does not contain any disclosure of the function of all the polypeptides" encompassed in the claims since "the genus of polypeptides that comprise the amino acid sequences is a large variable genus." Applicants courteously disagree with this contention.

The biochemistry of L-amino acid oxidases was known prior to the filing of the instant application. See, the paragraph bridging pages 3 and 4 of the instant specification. The motifs that impart the desired functionality of these proteins (for example, cytotoxicity) were also known to a skilled worker. Biological assays which can be used in the screening of variants/fragments with the desired functionality, for example, measurement of H_2O_2 generation in the presence of an L-amino acid, are also disclosed in the specification. See, page 4, lines 10-22.

The specification further provides specific disclosure of the polypeptides of the instant invention (i.e., polypeptides whose sequences are set forth in SEQ ID NO: 2, SEQ ID NO: 4 SEQ ID NO: 6; which are generically termed APIT) and methods for isolating such, for example, from crude ink of *Aplysia punctata*. See, page 5, lines 14-22. Biochemical, cellular, and pharmacological assay techniques for the identification of APIT variants are also described in detail. See, the paragraphs bridging pages 5 and 7 of the instant specification. In view of the mature state of the art at the time of the filing, it is submitted that a skilled worker could, using routine techniques, reliably and accurately screen for the species of compounds that are commensurate with the claimed invention. In this regard, Applicants' instant specification, coupled with a skilled worker's knowledge, provides adequate written description guidance as to the structural and functional aspects of the compounds claimed herein. Guidance for the structural aspect of the claimed compounds is, for example, provided by the individual amino acid sequences of the oxidase proteins and the polynucleotides encoding the same. Guidance for the functional aspect of the claimed polypeptides is, for example, provided by the disclosure of compounds having the capability to generate H_2O_2 (with respect to the biochemistry) and/or impart cytotoxicity (with respect to the functionality) in presence of certain substrates. Additionally, the reagents or tools for successfully isolating variants of the claimed compounds were of routine knowledge. For instance, using sequence similarity searches, a skilled artisan could isolate polypeptides that comprise at least 90% sequence identity with the polypeptide sequence of SEQ ID NO: 2. The functionality of the genus of compounds which satisfy the claimed structural parameter could be routinely screened using applicable *in vitro* or *in vivo* techniques, since the biology of L-amino oxidases, both at the molecular as well as physiological level, was well-established before the filing date of the instant application. For example, one could routinely use the isolation and assay techniques described in the Examples

to isolate compounds which are commensurate with the claimed invention. See, Examples 4 and 5, and particularly the disclosure contained in the paragraph bridging pages 42 and 43 of the instant specification. See also, the paragraph bridging pages 9 and 10 of the instant specification

Given this maturity in the field, any variant of the claimed compounds could be screened, allowing the skilled worker to practice the instant invention to its broadest possible scope. Nothing more than routine experimentation would be required and thus the metes and bounds of the claim would be adequately clear to one skilled in the art. It is therefore courteously submitted that Applicants' claims in the current form, with adequate support from the specification and the references cited therein fully comply with the statutory requirements under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Enablement

Regarding the lack of enablement rejection of claim 1, Applicants courteously submit that the specification, coupled with a skilled worker's knowledge, provides adequate guidance to make and use the polypeptides of the instant invention. "To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). For example, the present application provides polypeptide sequences [SEQ ID NOs:2, 4, and 6] and methods of obtaining other polypeptide sequences. See, *e.g.*, the paragraph bridging pages 5–8 and the disclosure contained in Figure 5 of the instant specification. In particular, techniques used to isolate sequences which are commensurate with the claims are disclosed in detail. See, the disclosure contained in Example 4. Methods of making and preparing the polypeptides of the instant invention are also provided. These include chemical synthetic means, as well as tools and reagents for the biological expression of the claimed polypeptides. It would be reasonably expected that such polypeptides could be isolated and used by one of ordinary skill in the art using the methods recited in the instant application. Other routinely used methods, assay techniques, and screening protocols have also been described. For example, see the disclosure contained in FIG 4 and the methodology described in Example 4.

Insufficient evidence has been presented to support the allegation that "the specification does not establish the desired activity of said proteins." The Office Action then proceeds to utilize Whisstock's (Whisstock et al., *Quarterly Reviews in Biophysics*, 2003, 36, pp 307-340) to support this contention. However, a copy of the Whisstock reference was not included with the Office Action, and the cited reference is also unavailable for download via private PAIR.

Applicants have nonetheless performed a cursory analysis of the ABSTRACT of the cited reference and find that the Examiner's contention to be misplaced. More specifically, Whisstock expressly states that similarity searches are relied upon for structure function prediction, which is commensurate with Applicants' own disclosure. For example, in the ABSTRACT section of Whisstock, a copy which is enclosed herewith, it is expressly stated:

> Many methods of function prediction rely on identifying similarity in sequence and/or structure between a protein of unknown function and one or more well-understood proteins. Alternative methods include inferring conservation patterns in members of a functionally uncharacterized family for which many sequences and structures are known. However, these inferences are tenuous. Such methods provide reasonable guesses at function, but are far from foolproof. It is therefore fortunate that the development of whole-organism approaches and comparative genomics permits other approaches to function prediction when the data are available. (Emphasis added)

Applicants courteously submit that the polypeptide sequences recited in the specification are not merely "other proteins" but are homologs and/or variants of the claimed polypeptides, which also comprise the structures and/or functions of the polypeptides exemplified in Applicants' instant specification. Express recitation of the structures and identification of the operative, partially operative, and/or inoperative fragments/variants are not required, given that such compounds could be routinely identified using the techniques disclosed in Applicants' own specification. Furthermore, as taught by Whisstock, homology-based searches can be *ab inito* used and relied-upon when investigating a functional role of a candidate polypeptide.

Regarding knowledge on how to make the polypeptide structures that share at least 90% sequence identity with a given polypeptide of SEQ. ID NO:2, it submitted that the specification provided detailed guidance on the techniques available to a skilled worker for routine identification of fragments and/or variants of the polypeptides which fall within the scope of the claims and retain the desired properties. More specifically, one could utilize PCR-coupled site directed mutagenesis technology for generating the

range of polynucleotide variants that are commensurate with the claims. Such variants could be routinely tested for claimed activity using expression/screening techniques described in the specification. For example, see, the disclosure contained in the Examples. Nothing more than routine experimentation would be required.

The Office Action then proceeds to allege that undue experimentation would be required to arrive at the majority of the polypeptides of the claimed genus. Firstly, it is submitted that Examiner has not presented any evidence to reasonably doubt the objective truth of the claims. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein. See *Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made. There are especially weak in the face of the showing that the field of L-amino acid oxidases and their homologs, including methods for assaying the biological activity of such compounds, were all conventionally appreciated in the art well before the filing date of the instant application.

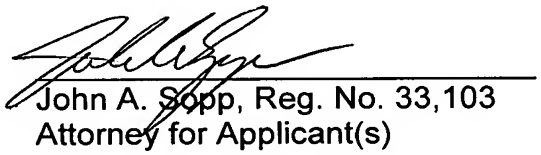
Applicants therefore courteously submit that the claims are enabled and that the USPTO has failed to meet its burden of establishing lack of enablement.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine within the art. The statute requires nothing more. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,



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Date: May 14, 2007

Encl: ABSTRACT of Whisstock et al. (2003)

1: Q Rev Biophys. 2003 Aug;36(3):307-40.

Prediction of protein function from protein sequence and structure.

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The sequence of a genome contains the plans of the possible life of an organism, but implementation of genetic information depends on the functions of the proteins and nucleic acids that it encodes. Many individual proteins of known sequence and structure present challenges to the understanding of their function. In particular, a number of genes responsible for diseases have been identified but their specific functions are unknown. Whole-genome sequencing projects are a major source of proteins of unknown function. Annotation of a genome involves assignment of functions to gene products, in most cases on the basis of amino-acid sequence alone. 3D structure can aid the assignment of function, motivating the challenge of structural genomics projects to make structural information available for novel uncharacterized proteins. Structure-based identification of homologues often succeeds where sequence-alone-based methods fail, because in many cases evolution retains the folding pattern long after sequence similarity becomes undetectable. Nevertheless, prediction of protein function from sequence and structure is a difficult problem, because homologous proteins often have different functions. Many methods of function prediction rely on identifying similarity in sequence and/or structure between a protein of unknown function and one or more well-understood proteins. Alternative methods include inferring conservation patterns in members of a functionally uncharacterized family for which many sequences and structures are known. However, these inferences are tenuous. Such methods provide reasonable guesses at function, but are far from foolproof. It is therefore fortunate that the development of whole-organism approaches and comparative genomics permits other approaches to function prediction when the data are available. These include the use of protein-protein interaction patterns, and correlations between occurrences of related proteins in different organisms, as indicators of functional properties. Even if it is possible to ascribe a particular function to a gene product, the protein may have multiple functions. A fundamental problem is that function is in many cases an ill-defined concept. In this article we review the state of the art in function prediction and describe some of the underlying difficulties and successes.

PMID: 15029827 [PubMed - indexed for MEDLINE]

Links

Related Links

Protein structure prediction and structural genomics. [Science. 2001]

SUPFAM--a database of potential protein superfamily relationships derived by comparing sequence-based and structure-based families: implications for structural genomics and function annotation in genomes. [Nucleic Acids Res. 2002]

Method for prediction of protein function from sequence using the sequence-to-structure-to-function paradigm with application to glutaredoxins/thioredoxins and T1 ribonucleases. [J Mol Biol. 1998]

Systematic analysis of human kinase genes: a large number of genes and alternative splicing events result in functional and structural diversity. [BMC Bioinformatics. 2005]

Protein structure prediction and analysis as a tool for functional genomics. [Brief Bioinform. 2003]

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